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THIENYL COMPOUNDSTechnical Field

- This invention relates to novel spiroazabicyclic heterocyclic amines or  
 5 pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy.

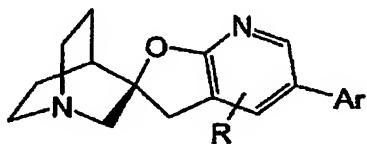
Background Of The Invention

The use of compounds which bind to nicotinic acetylcholine receptors for the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's  
 10 disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease is discussed in McDonald *et al.*, (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams *et al.*, (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

Description of the Invention

This invention comprises compounds that are potent ligands for nicotinic acetylcholine receptors (nAChR's).

Compounds of the inventions are those in accord with formula I:



I

and pharmaceutically-acceptable salts thereof, wherein

Ar is selected from a 2-, or 3-linked thiényl or benzo-fused thiényl substituted with 0, 1, 2 or 3 substituents independently selected at each occurrence from C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> halogenated alkyl, C<sub>1-4</sub> oxygenated alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, halogen, -CO<sub>2</sub>R<sup>1</sup>, -C(O)R<sup>1</sup>, -CN, -NO<sub>2</sub>, -NR<sup>1</sup>R<sup>2</sup>.

R<sup>1</sup> and R<sup>2</sup> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R is a substituent selected from hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub> halogenated alkyl, C<sub>1-4</sub> oxygenated alkyl, or halogen.

Particular compounds of the invention are those wherein R is hydrogen and Ar is a 2-, or 3-linked thiienyl having 0 or 1 substituents selected from methyl, ethyl, or halogen.

Particular compounds of the invention include:

- (2'R)-5'-(thiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
5 (2'R)-5'-(thiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
(2'R)-5'-(benzo[b]thiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
10 (2'R)-5'-(benzo[b]thiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
(2'R)-5'-(5-methylthiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
15 (2'R)-5'-(4-methylthiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
(2'R)-5'-(5-chlorothiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
20 (2'R)-5'-(5-chlorothiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine].

Other particular compounds of the invention include:

- (2'R)-5'-(5-fluorothiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
25 (2'R)-5'-(5-bromothiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
(2'R)-5'-(5-fluorothiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
30 (2'R)-5'-(5-bromothiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];  
(2'R)-4-{spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridin-5'-yl]}thiophene-2-carbonitrile;  
(2'R)-5-{spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridin-5'-yl]}thiophene-2-carbonitrile.

In another aspect the invention relates to compounds according to formula I and their use in therapy and compositions containing them.

In a further aspect the invention relates to compounds according to formula I wherein one or more of the atoms is labelled with a radioisotope of the same element. In a particular form of this aspect of the invention the compound of formula I is labelled with tritium

- 15 In a particular aspect the invention relates to the use of compounds according to formula I for the therapy of diseases mediated through the action of nicotinic acetylcholine receptors. A more particular aspect of the invention relates to the use of compounds of formula I for the therapy of diseases mediated through the action of  $\alpha_7$  nicotinic acetylcholine receptors.

- 10 Another aspect of the invention relates to a pharmaceutical composition comprising a compound as described above, and a pharmaceutically-acceptable diluent or carrier.

Another aspect of the invention relates to the above pharmaceutical composition for use in the treatment of prophylaxis of human diseases or conditions in which activation of the  $\alpha_7$  nicotinic receptor beneficial.

- 15 Another aspect of the invention relates to the above pharmaceutical composition for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

Another aspect of the invention relates to the above pharmaceutical composition for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, or mania or manic depression Parkinson's disease, Huntington's disease,

- 20 Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, craving, pain, and for ulcerative colitis.

Another aspect of the invention relates to a use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the  $\alpha_7$  nicotinic receptor is beneficial.

Another aspect of the invention relates to a use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

- 30 Another aspect of the invention relates to the above use, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder.

Another aspect of the invention relates to the above use, wherein the disorder is anxiety, schizophrenia, or mania or manic depression.

Another aspect of the invention relates to the above use, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

Another aspect of the invention relates to the use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, craving, pain, and for ulcerative colitis.

10 Another aspect of the invention relates to a method of treatment or prophylaxis of human diseases or conditions in which activation of the  $\alpha_7$  nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound as described above.

15 Another aspect of the invention relates to a method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as described above.

Another aspect of the invention relates to the above method, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, or Attention Deficit Hyperactivity Disorder.

20 Another aspect of the invention relates to the above method, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

Another aspect of the invention relates to the above method, wherein the disorder is anxiety, schizophrenia or mania or manic depression.

25 Another aspect of the invention relates to a method of treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction, craving, pain, and for ulcerative colitis, which comprises administering a therapeutically effective amount of a compound as described above.

30 Compounds structurally related to the compounds of the present invention are 5-aryl spirofuropyridines described in WO 99/03859, for example the compounds of Example 3 and Example 21 therein. Relative to these compounds, the compounds of the present invention possess surprisingly advantageous properties. In particular, the present compounds have the

advantage of surprisingly enhanced potency in binding to the  $\alpha_7$  nAChR, as well as enhanced selectivity versus the  $\alpha_4$  receptor. The significantly greater potency and selectivity of compounds of the present invention result in advantageous properties that distinguish the use of such compounds as pharmaceutical agents by lowering the efficacious dose, lengthening  
5 the duration of action, and improving side effect profile.

A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof or a  
10 pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are  
15 administered at a daily dosage of from about 0.1 mg to about 20 mg/kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

20 The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture  
25 with an inert pharmaceutically acceptable diluent or carrier.

Examples of diluents and carriers are:

- for tablets and dragees: lactose, starch, talc, stearic acid;
- for capsules: tartaric acid or lactose;
- for injectable solutions: water, alcohols, glycerin, vegetable oils;
- for suppositories: natural or hardened oils or waxes.

30 There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the above mentioned diseases 5 or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically acceptable salt thereof, to a patient.

Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the  $\alpha_7$  nAChR 10 (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over compounds which are or are also agonists of the  $\alpha_4$  nAChR subtype. Therefore, compounds which are selective for the  $\alpha_7$  nAChR subtype are preferred. The compounds of the invention are indicated as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic 15 disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the 20 treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in inducing the cessation of smoking, craving, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

25 It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

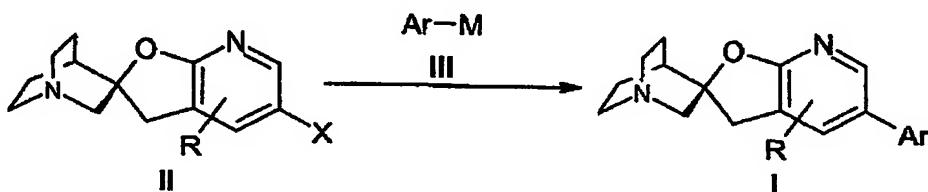
As used herein, the term "C<sub>1-4</sub> alkyl" refers to a straight-chained, branched, or cyclic C<sub>1-4</sub>alkyl group.

30 As used herein the term "C<sub>1-4</sub> halogenated alkyl" refers to a C<sub>1-4</sub>alkyl group substituted with 1, 2, or 3 halogen atoms.

As used herein the term "C<sub>1-4</sub> oxygenated alkyl" refers to a C<sub>1-4</sub>hydroxyalkyl or C<sub>1-4</sub> alkoxyalkyl group.

**Methods of Preparation**

Compounds of formula I may be prepared according to the methods known to persons skilled in the art of synthetic organic chemistry. Methods which may be used for the synthesis of compounds of formula I include the method outlined in Scheme 1. Unless otherwise noted Ar and R in Scheme 1 are as defined above for Formula 1.

**Scheme 1**

10

Compounds of formula I may be prepared from compounds of formula II wherein X represents a halogen or  $\text{OSO}_2\text{CF}_3$  substituent by reaction with an appropriate organometallic compound of formula III in the presence of a suitable organometallic catalyst and solvent.

- Suitable compounds of formula III include boronic acids, in which M represents  $\text{B}(\text{OH})_2$ ,  
15 boronic acid esters, in which M represents  $\text{B}(\text{OY})_2$ , where Y represents a suitable acyclic or cyclic alkyl or aryl group, and organotin compounds, in which M represents a suitable trialkylstannylyl group, for example trimethylstannylyl or tri-n-butylstannylyl. Suitable organometallic catalysts include palladium (0) complexes, for example tetrakis(triphenylphosphine)palladium(0) or a combination of  
20 tris(dibenzylideneacetone)dipalladium(0) and a suitable triarylphosphine or triarylsulfine ligand, for example triphenylphosphine, tri(*o*-tolyl)phosphine or triphenylarsine. Suitable solvents include inert ether solvents, for example 1,2-dimethoxyethane, tetrahydrofuran, or 1,4-dioxane, or alcohols, such as ethanol, or mixtures thereof. If the compound of formula III is a boronic acid, the presence of a suitable base in addition to the other reagents is preferred.  
25 Suitable bases include sodium carbonate, cesium carbonate, and barium hydroxide. The reaction is carried out at a temperature of 0-120°C, and preferably at a temperature of 60-120 °C.

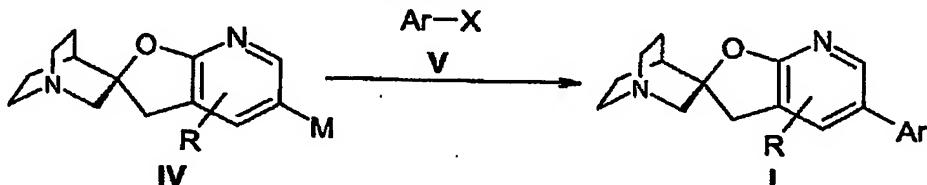
Certain compounds of formula II wherein X represents halogen may be prepared from compounds of formula II wherein X represents hydrogen by reaction with a suitable

halogenating agent in a suitable solvent. Suitable halogenating agents include bromine. Suitable solvents include acetic acid. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 0-25 °C. Compounds of formula II may be prepared by the methods described in application WO99/03859.

5 Compounds of formula II wherein X represents OSO<sub>2</sub>CF<sub>3</sub> may be prepared from compounds of formula II wherein X represents OH by reaction with trifluoromethanesulfonic anhydride or other trifluoromethanesulfonylating agent in the presence of a base and a suitable solvent. Suitable bases include pyridine, and 2,6-di-t-butylpyridine. The reaction is preferably performed at a temperature of -78 to 120 °C, and most preferably at a temperature of -78 to  
10 0 °C.

Compounds of formula III are commercially available, are described in the literature of synthetic organic chemistry, or may be prepared by methods known to one skilled in the art of synthetic organic chemistry. For example, compounds of formula III in which M represents B(OH)<sub>2</sub> may be prepared from suitable aromatic compounds having hydrogen or halogen groups, via conversion to the corresponding aryllithium or arylmagnesium compounds followed by reaction with trialkylborate and subsequent hydrolysis of the resulting borate ester. Similarly, suitable aromatic compounds having hydrogen or halogen groups may be converted to compounds of formula III in which M represents a trialkylstannyl group via conversion to the corresponding aryllithium or arylmagnesium compounds followed by reaction with an appropriate trialkylstannyl halide. The formation of the aryllithium or arylmagnesium compound is performed in a suitable inert solvent, for example, tetrahydrofuran. Alternatively, suitable aromatic compounds having halogen or OSO<sub>2</sub>CF<sub>3</sub>, may be converted to compounds of formula III in which M represents B(OH)<sub>2</sub> via reaction with bis(pinacolato)diboron and an organometallic catalyst, followed by hydrolysis of the resulting borate ester, or to compounds of formula III in which M represents a trialkylstannyl group via reaction with the appropriate bis(trialkyltin) in the presence of a suitable organometallic catalyst. The reaction is performed in a suitable inert solvent, for example tetrahydrofuran, and suitable organometallic catalyst include, for example tetrakis(triphenylphosphine). The reaction is performed at a temperature of about 0 °C to about 150 °C, preferably about 20 °C to about 100 °C. For typical procedures for effecting such conversions, see, for example, *Organic Syntheses*, 1963, Coll. Vol. 4, 68; *J. Org. Chem.* 1995, 60, 7508.

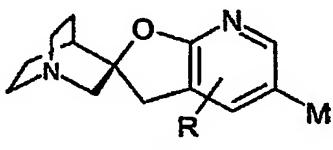
An alternative synthesis of compounds of formula I is outlined in Scheme 2. Unless otherwise noted Ar, R, M and X in Scheme 2 are as defined above for Scheme 1, and Ar and R are as defined in Formula I. The conditions for effecting the preparation described in Scheme 2 would be similar to those under which the preparations described in Scheme 1 would be performed with corresponding M and X groups.



Scheme 2

- Compounds of formula IV in which M represents  $B(OH)_2$  may be prepared from compounds of formula II in which X is halogen, via conversion to the corresponding 10 aryllithium or arylmagnesium compounds followed by reaction with a trialkylborate and subsequent hydrolysis of the resulting borate ester. Similarly, compounds of formula IV in which M represents  $SnR^3_3$ , and  $R^3$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group may be prepared from compounds of formula II in which X is halogen, via conversion to the corresponding aryllithium or arylmagnesium compounds followed by reaction with an appropriate 15 trialkylstannyl halide. The formation of the aryllithium or arylmagnesium compound is performed in a suitable inert solvent, for example, tetrahydrofuran, and Alternatively, compounds of formula IV in which M represents  $B(OH)_2$  may be prepared from compounds of formula II in which X represents halogen or  $OSO_2CF_3$  via reaction with bis(pinacolato)diboron and an organometallic catalyst, followed by hydrolysis of the resulting 20 borate ester, and compounds of formula IV in which M represents  $SnR^3_3$  and  $R^3$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group may be prepared from compounds of formula II in which X represents halogen or  $OSO_2CF_3$  via reaction with the appropriate bis(trialkyltin)  $R^3_3SnSnR^3_3$  25 in the presence of a suitable organometallic catalyst. The reaction is performed in a suitable inert solvent, for example tetrahydrofuran, and suitable organometallic catalyst include, for example tetrakis(triphenylphosphine). The reaction is performed at a temperature of about 0 °C to about 150 °C, preferably about 20 °C to about 100 °C. For typical procedures for effecting such conversions, see, for example, *Organic Syntheses*, 1963, Coll. Vol. 4, 68; *J. Org. Chem.* 1995, 60, 7508.

A further aspect of the invention therefore relates to intermediates. Such intermediates are useful in the synthesis of compounds of formula I, and other compounds that bind nicotinic acetylcholine receptors. Particularly useful intermediates are compounds of formula IV below:



5

IV

wherein:

M represents  $B(OH)_2$ ,  $B(OR^3)_2$  or  $SnR^3_3$ ;

R is a substituent selected from hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ halogenated alkyl,  $C_{1-4}$ oxygenated alkyl, or halogen;

10  $R^3$  represents a  $C_{1-C_6}$  alkyl group.

Particular compounds that are useful intermediates include:

( $2'R$ )- $5'$ -trimethylstannyl-spiro[1-azabicyclo[2.2.2]octane-3,2'( $3'H$ )-furo[2,3-b]pyridine].

It will be appreciated by one skilled in the art that certain optional aromatic  
15 substituents in the compounds of the invention may be introduced by employing aromatic substitution reactions, or functional group transformations to modify an existing substituent, or a combination thereof. Such reactions may be effected either prior to or immediately following the processes mentioned above, and are included as part of the process aspect of the invention. The reagents and reaction conditions for such procedures are known in the art.

20 Specific examples of procedures which may be employed include, but are not limited to, electrophilic functionalisation of an aromatic ring, for example via nitration, halogenation, or acylation; transformation of a nitro group to an amino group, for example via reduction, such as by catalytic hydrogenation; acylation, alkylation, sulfonylation of an amino or hydroxyl group; replacement of an amino group by another functional group via conversion to an  
25 intermediate diazonium salt followed by nucleophilic or free radical substitution of the diazonium salt; or replacement of a halogen by another functional group, for example via nucleophilic or organometallically-catalysed substitution reactions.

Where necessary, hydroxy, amino, or other reactive groups may be protected using a protecting group as described in the standard text "Protecting groups in Organic Synthesis",  
30 3<sup>rd</sup> Edition (1999) by Greene and Wuts.

The above described reactions, unless otherwise noted, are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

Unless otherwise stated, the above described reactions are conducted under an inert 5 atmosphere, preferably under a nitrogen atmosphere.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed 10 with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, 15 tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by 20 separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallisation, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemisation.

25 **Pharmacology**

The pharmacological activity of compounds of the invention may be measured using the tests set out below:

**Test A - Assay for affinity at  $\alpha 7$  nAChR subtype**

[<sup>125</sup>I]- $\alpha$ -Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi 30 were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; MgCl<sub>2</sub> 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 g, the supernatant was saved

and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12000 g, washed, and resuspended in HB. Membranes (30–80 µg) were incubated with 5 nM [<sup>125</sup>I]α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM CaCl<sub>2</sub> or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethyl ether)] for 2 hours at 21 °C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per minute). Nonspecific binding was described by 100 µM (–)-nicotine, and specific binding was typically 75%.

**Test B - Assay for affinity to the α<sub>4</sub> nAChR subtype**

[<sup>3</sup>H]-(-)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenized as in the [<sup>125</sup>I]α-BTX binding assay, centrifuged for 20 minutes at 12,000 x g, washed twice, and then resuspended in HB containing 100 µM diisopropyl fluorophosphate. After 20 minutes at 4 °C, membranes (approximately 0.5 mg) were incubated with 3 nM [<sup>3</sup>H]-(-)-nicotine, test drug, 1 µM atropine, and either 2 mM CaCl<sub>2</sub> or 0.5 mM EGTA for 1 h at 4 °C, and then filtered over Whatman glass fiber filters (thickness C) (pretreated for 1 h with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 µM carbachol, and specific binding was typically 84%.

**Binding data analysis for Tests A and B**

IC<sub>50</sub> values and pseudo Hill coefficients (nH) were calculated using the non-linear curve-fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding KD values of 1.67 and 1.70 nM for the [<sup>125</sup>I]-α-BTX and [<sup>3</sup>H]-(-)-nicotine ligands respectively. Ki values were estimated using the general Cheng-Prusoff equation:

$$Ki = [IC_{50}] / ((2 + ([ligand]/[KD])n)/n - 1)$$

where a value of n=1 was used whenever nH<1.5 and a value of n=2 was used when nH≥1.5. Samples were assayed in triplicate and were typically ±5%. Ki values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (Ki) of less than 1000 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

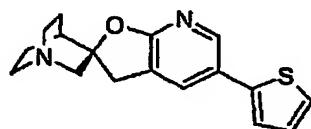
Examples

5        Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer and are reported as m/z for the parent molecular ion with its relative intensity. Room temperature refers to 20–25 °C.      Radiolabelled forms of compounds of the examples are useful in a screen for the discovery of novel medicinal compounds which bind to and  
10 modulate the activity, via agonism, partial agonism, or antagonism, of the  $\alpha_7$  nicotinic acetylcholine receptor. Such radiolabelled compounds are synthesized either by incorporating radiolabelled starting materials or, in the case of tritium, exchange of hydrogen for tritium by known methods. Known methods include (1) electrophilic halogenation, followed by reduction of the halogen in the presence of a tritium source, for example, by hydrogenation  
15 with tritium gas in the presence of a palladium catalyst, or (2) exchange of hydrogen for tritium performed in the presence of tritium gas and a suitable organometallic (e.g. palladium) catalyst.

Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer  
20 and are reported as m/z for the parent molecular ion with its relative intensity. Room temperature refers to 20–25 °C. 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and other precursors were prepared as described in international patent application WO 99/03859.

25        Example 1

(2'R)-5'-(Thiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

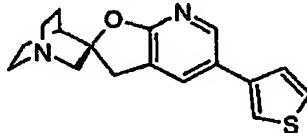


(2'R)-5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]  
30 (162 mg, 0.55 mmol), 2-thiopheneboronic acid (0.39 g, 0.84 mmol), tetrakis(triphenylphosphine)palladium (0) (42 mg, 0.036 mmol), and sodium carbonate (0.38 g,

3.6 mmol) were placed in a tube under nitrogen. Water (1 mL), ethanol (1 mL) and tetrahydrofuran (4 mL) were added. The mixture was then heated at 70 °C and stirred under nitrogen for 24 h. The mixture was then evaporated under vacuum and the residue from evaporation was partitioned between dilute aqueous sodium hydroxide and chloroform, the layers were separated, and the aqueous layer was further extracted with chloroform. The chloroform extract was dried (magnesium sulfate), filtered, and evaporated. The residue was purified by reverse phase HPLC on a Waters Novapak-HR C<sub>18</sub> Column using a gradient of 0-70% acetonitrile / water (each solvent containing 0.1% trifluoroacetic acid as a buffer) as the eluant. The product-containing fractions were evaporated, then the residue was dissolved in methanol. Excess concentrated hydrochloric acid was added, and the solution was evaporated to give the dihydrochloride salt of the title compound (117 mg) as a colourless solid; m/z 299 (100%, MH<sup>+</sup>).

#### Example 2

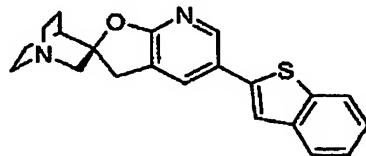
15 (2'R)-5'-(Thiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]



Prepared by a method analogous to that described for the preparation of Example 1 from (2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and 3-thiopheneboronic acid. The dihydrochloride salt of the title compound was as a colourless solid; m/z 299 (100%, MH<sup>+</sup>).

#### Example 3

(2'R)-5'-(Benz[b]thiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]



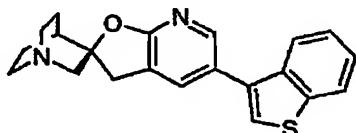
25

Prepared by a method analogous to that described for the preparation of Example 1 from (2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and

benzo[b]thiophene-2-boronic acid. The compound was purified by flash chromatography using a gradient of ammoniated methanol in chloroform and obtained as a pale solid; m/z 349 (100%, MH<sup>+</sup>).

5    **Example 4**

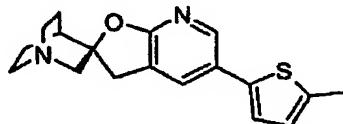
(2'R)-5'-(Benzo[b]thiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]



Prepared by a method analogous to that described for the preparation of Example 1  
 10 from (2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and benzo[b]thiophene-3-boronic acid. The compound was purified by flash chromatography using a gradient of ammoniated methanol in chloroform and obtained as a pale solid; m/z 349 (100%, MH<sup>+</sup>).

15    **Example 5**

(2'R)-5'-(5-Methylthiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

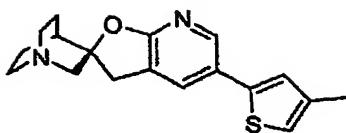


Prepared by a method analogous to that described for the preparation of Example 1  
 20 from (2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and 5-methylthiophene-2-boronic acid. The compound was purified by flash chromatography using a gradient of ammoniated methanol in chloroform and obtained as a pale solid; m/z 313 (100%, MH<sup>+</sup>).

**Example 6**

25    (2'R)-5'-(4-Methylthiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

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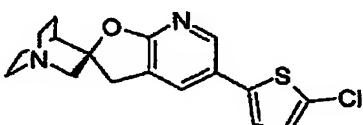


Prepared by a method analogous to that described for the preparation of Example 1 from (2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and 4-methyl-thiophene-2-boronic acid. The title compound was obtained as a colourless solid; m/e 313 (MH<sup>+</sup>).

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**Example 7**

(2'R)-5'-(5-Chlorothiophen-2-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]



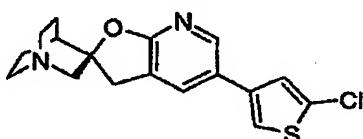
10

Prepared by a method analogous to that described for the preparation of Example 1 from (2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and 5-chlorothiophene-2-boronic acid. The dihydrochloride salt of the title compound was isolated a colourless solid; m/e 333 (MH<sup>+</sup>).

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**Example 8**

(2'R)-5'-(5-Chlorothiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]



20

(a) (2'R)-5'-Trimethylstannylspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(2'R)-5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (690 mg, 2.34 mmol), hexamethylditin (1.225 g, 0.27 mmol) and tetrakis(triphenylphosphine)palladium (0) (266 mg, 0.027 mmol) were mixed with 10 mL of toluene and sealed under nitrogen. The mixture was stirred and heated at 120 °C under nitrogen for 4 h. The mixture was allowed to cool, then filtered through Celite. The filtrate was diluted with chloroform, washed with saturated sodium bicarbonate, dried through MgSO<sub>4</sub>, filtered, and then the solvent was evaporated. The compound was purified by flash chromatography using a gradient of ammoniated methanol in chloroform to give the sub-title compound as a pale solid; m/e 377 379 381 (M<sup>+</sup>).

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(b) 4-Bromo-2-chlorothiophene

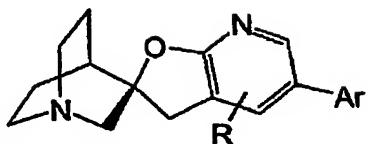
3,5-Dibromothiophene (1.74 g, 7.19 mmol) in anhydrous ether (15 mL) was stirred at -78 °C under nitrogen. n-Butyllithium (1.6M, 4.95 mL, 7.91 mmol) was added, and stirring was continued at -78 °C for 15 min. Then, hexachloroethane (1.87 g, 7.91 mmol) was added, and stirring was continued for another 30 min. The reaction mixture was quenched with saturated ammonium chloride, diluted with ether, washed with water and brine, then dried through MgSO<sub>4</sub> and filtered. Then the solvent was evaporated to give a brown oil which was purified by flash chromatography using a gradient of ammoniated methanol in chloroform as the eluant to give the sub-title compound as a light yellow oil (1.07 g); m/e 196 198 (M<sup>+</sup>).

10 (c) (2'R)-5'-(5-Chlorothiophen-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2.3-b]pyridine]

(2'R)-5'-Trimethylstannylspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2.3-b]pyridine] (140 mg, 0.37 mmol), 3-bromo-5-chloro-thiophene (88mg, 0.44 mmol) and tetrakis(triphenylphosphine)palladium (0) (43mg, 0.037 mmol) were dissolved in toluene (2 mL) and sealed under nitrogen. The mixture was stirred and heated at 120 °C under nitrogen overnight. The mixture was allowed to cool, then filtered through Celite. The filtrate was diluted with chloroform, washed with saturated sodium bicarbonate, dried through MgSO<sub>4</sub>, filtered, and then the solvent was evaporated. The compound was purified by flash chromatography followed by reverse phase HPLC on a Waters Novapak-HR C<sub>18</sub> Column using a gradient of 0 - 65% acetonitrile/water (each solvent containing 0.1% trifluoroacetic acid as a buffer) as the eluant. The product-containing collections were evaporated. The residue was dissolved in methanol, then excess 1N hydrochloric acid was added, and the solvent was evaporated to give the dihydrochloride salt of the title compound (35 mg) as a colourless solid; m/e 333 335 (MH<sup>+</sup>).

**CLAIMS**

1. A compound having the formula:



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and pharmaceutically-acceptable salts thereof, wherein

Ar is selected from a 2-, or 3-linked thienyl or benzo-fused thienyl substituted with 0, 1, 2 or 3 substituents independently selected at each occurrence from C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> halogenated alkyl, C<sub>1-4</sub> oxygenated alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, halogen, -CO<sub>2</sub>R<sup>1</sup>,

10 -C(O)R<sup>1</sup>, -CN, -NO<sub>2</sub>, -NR<sup>1</sup>R<sup>2</sup>.

R<sup>1</sup> and R<sup>2</sup> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R is a substituent selected from hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub> halogenated alkyl, C<sub>1-4</sub> oxygenated alkyl, or halogen.

15 2. A compound according to Claim 1 or a pharmaceutically-acceptable salt thereof, wherein:

Ar is a 2-, or 3-linked thienyl having 0 or 1 substituents selected from methyl, ethyl, or halogen, and

R is hydrogen.

20

3. A pharmaceutical composition comprising a compound according to Claim 1, and a pharmaceutically-acceptable diluent or carrier.

4. The pharmaceutical composition according to Claim 3, for use in the treatment of

25 prophylaxis of human diseases or conditions in which activation of the  $\alpha_7$  nicotinic receptor is beneficial.

5. The pharmaceutical composition according to Claim 3, for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

30

6. The pharmaceutical composition according to Claim 3, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, or mania or manic depression Parkinson's disease, Huntington's disease, Tourette's syndrome,

5 neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, craving, pain, and for ulcerative colitis.

7. Use of a compound according to Claim 1, in the manufacture of a medicament for the  
10 treatment or prophylaxis of human diseases or conditions in which activation of the  $\alpha_7$  nicotinic receptor is beneficial.

8. Use of a compound according to Claim 1, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

15 9. The use according to Claim 8, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder.

20 10. The use according to Claim 8, wherein the disorder is anxiety, schizophrenia, or mania or manic depression.

11. The use as claimed in claim 8, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

25 12. Use of a compound according to Claim 1 in the manufacture of a medicament for the treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, craving, pain, and for ulcerative colitis.

13. A method of treatment or prophylaxis of human diseases or conditions in which activation of the  $\alpha_7$  nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound according to Claim 1.

5 14. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound according to Claim 1.

10 15. The method according to Claim 14, wherein said psychotic disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder Parkinson's disease, Huntington's disease, Tourette's syndrome, a neurodegenerative disorder in which there is loss of cholinergic synapses anxiety, schizophrenia or mania or manic depression.

15 16. A method of treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction, craving, pain, and for ulcerative colitis, which comprises administering a therapeutically effective amount of a compound according to Claim 1.

20 17. A compound according to Claim 1, wherein one or more of the atoms is labelled with a radioisotope of the same element.

18. A compound according to Claim 17, wherein the radioisotope is tritium.

25 19. The use of a compound according to Claim 18, in a screen for the discovery of novel medicinal compounds which bind to and modulate the activity, via agonism, partial agonism, or antagonism, of the  $\alpha_7$  nicotinic acetylcholine receptor.

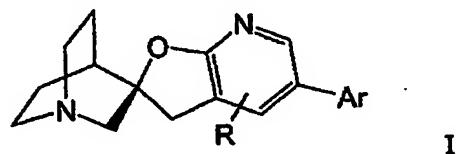


## A B S T R A C T

TITLE: THIENYL COMPOUNDS

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A compound having the formula I:



and pharmaceutically-acceptable salts thereof, wherein Ar and R are as defined in the specification, compositions containing such compounds and the use of such compounds and  
10 compositions for use in therapy.

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